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Dated: September 24, 2004

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(54) New dipeptide-derivative or dipeptide-analog compounds useful as sweetening agents, their formulation process

(57) This invention relates to compounds with the general formula:
[see original for formula]
where:
R is a hydrocarbon group having from four to thirteen saturated or unsaturated carbon atoms, which may be cyclic, acyclic, or a combination;
n is equal to 1 or 2;
and R' is represented by the following formula:
[see original for formula]
where Y is selected from the group comprising $COOCH_3$, $COOC_2H_5$, CH_3, CH_2OH, $CON(CH_3)_2$, C_6H_5, 2-furyl, and H, and where Z is selected from the group comprising $CH_2C_6H_5$, C_6H_5, n-C_4H_9, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, COOfenchyl, and CONHR", where R" is selected from the group comprising CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH(CH_3)COOCH_3$, $CH(c\text{-}C_3H_5)_2$, $CH(c\text{-}C_3H_5)C(CH_3)_3$, fenchyl, 2,6-dimethylcyclohexyl, 2,2,5,5-tetramethylcyclopentyl, and 2,2,4,4-tetramethyl-3-thietanyl;
and their physiologically acceptable salts.
These compounds are useful as sweetening agents.

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This invention relates to new sweet dipeptide-derivative or dipeptide-analog compounds, useful as sweetening agents, as well as their formulation process.

These new compounds are particularly useful for sweetening various products, particularly foods, beverages, confectionery, pastries, chewing gums, hygiene products, and toilet articles, as well as cosmetic, pharmaceutical, and veterinary products.

It is known that, for a sweetening agent to be usable on an industrial scale, it must have both intense sweetening power, which limits the cost of use, and satisfactory stability, i.e., be compatible with the conditions of use.

Of the sweetening agents currently on the market, a dipeptide derivative, L-aspartyl-L-phenylalanine methyl ester, known as aspartame, with the following formula:

[see original for formula]

is the most used (U.S. 3,475,403). The relatively weak sweetening power of this compound is approximately 120 to 180 times that of sucrose by weight. Despite its excellent organoleptic qualities, the primary drawback of this compound is that it is expensive, due to its relatively weak sweetening intensity, and that it has fairly low stability under the usual conditions of use for sweeteners, which greatly limits its industrial fields of application.

Consequently, it seemed necessary for the food industry to have a new sweetening agent with intense sweetening activity, to lower the cost price, and that would be more stable than aspartame. One of the advantages of aspartame is its chemical composition based on two natural amino acids, L-aspartic acid and L-phenylalanine. Many sweet dipeptides or dipeptide analogs have subsequently been synthesized (for example, see J.M. Janusz, in Progress in Sweeteners, Ed. T.H. Grenby, Elsevier, London, 1989, pp. 1-46), but, to date, except for aspartame and perhaps alitame (EP-034 876), none has seemed to meet the primary requirements for a sweetener, i.e., good organoleptic qualities, strong sweetening intensity to decrease the cost of use, and sufficient stability.

In document EP-0 338 946, the Applicants proposed sweetening agents derived from natural N-hydrocarbon amino acids, with the following general formula:

[see original for formula]

where the R radical is a hydrocarbon group with five to thirteen saturated or unsaturated, carbon atoms, which may be cyclic, acyclic, or a combination, where the R' radical is a 4-cyanophenyl, 2-cyanopyrid-5-yl, or 2-cyanopyrimidin-5-yl group, and where n is equal to 1 or 2.

Although, in the aforesaid formula, in order to achieve an intense sweetening effect, it was thought to be essential that the R' group be a specific radical, such as those indicated in document EP-0 338 946, it has unexpectedly been found that new groups, with no structural analogy to those in the R' group, as initially defined, could substitute them while maintaining their sweetening properties.

Therefore, the purpose of this invention is to provide new sweetening agents derived from N-hydrocarbon amino acids, which have excellent organoleptic qualities combined with very intense sweetening power – up to 10,000 times the sweetening power of sucrose by weight – and greater stability than aspartame in an acid or neutral solution, thus with extended possibilities for use in food preparations compared to aspartame.

The compounds of this invention have the following general formula:

[see original for formula]

where:
R is a hydrocarbon group with four to thirteen saturated or unsaturated carbon atoms, which may be cyclic, acyclic, or a combination;
n is equal to 1 or 2;
and R' is represented by the following formula:

[see original for formula]

where Y is selected from the group comprising $COOCH_3$, $COOC_2H_5$, CH_3, CH_2OH, $CON(CH_3)_2$, C_6H_5, 2-furyl, and H, and where Z is selected from the group comprising $CH_2C_6H_5$, C_6H_5, *n*-C_4H_9, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, COOfenchyl, and CONHR", where R" is selected from the group comprising CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH(CH_3)COOCH_3$, $CH(c\text{-}C_3H_5)_2$, $CH(c\text{-}C_3H_5)C(CH_3)_3$, fenchyl, 2,6-dimethylcyclohexyl, 2,2,5,5-tetramethylcyclopentyl, and 2,2,4,4-tetramethyl-3-thietanyl.

These compounds may occur in the free form or in the form of physiologically acceptable salts.

In the context of this invention, a hydrocarbon group is understood to mean any saturated or unsaturated group composed of carbon and hydrogen atoms. The saturated group may be an alkyl or cycloalkyl group, and the unsaturated group may be an alkenyl group with 1 to 3 double bonds or an aryl group. A combination group is understood to mean a hydrocarbon group comprising at least one acyclic part and at least one cyclic part. For example, a cycloalkylalkyl or arylalkyl group is such a group.

Furthermore, the alkyl or alkenyl groups may be linear or branched chain groups.

A linear chain alkyl group is, for example, a $CH_3CH_2CH_2CH_2$ group, and a branched chain alkyl group is, for example, a $(CH_3)_2CHCH_2$ or $(CH_3)_3CCH_2CH_2$ group.

A cycloalkyl group is, for example, a *c*-C_6H_{11} group.

A cycloalkylalkyl group is, for example, a *c*-$C_3H_5CH_2CH_2$, *c*-$C_4H_7CH_2CH_2$ or *c*-$C_5H_9CH_2$ group.

An alkenyl group is, for example a $(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)$ CH_2CH_2 or 4-isopropenyl-1-cyclohexenylethyl group.

An arylalkyl group is, for example, a $C_6H_5C(CH_3)_2CH_2$ or $C_6H_5CH_2C(CH_3)_2CH_2$ group.

In a preferred embodiment, the compounds of the invention are L-aspartic acid derivatives (n = 1) with the following general formula:

[see original for formula]

where the R, Y, and Z radicals meet the aforesaid definitions.

When Y is $COOCH_3$ and Z is $CH_2C_6H_5$, the resultant compounds are aspartame derivatives and constitute a particularly advantageous embodiment of the invention. These compounds have the following general formula:

[see original for formula]

where R is preferably selected from the group comprising $CH_3CH_2CH_2CH_2$, $(CH_3)_2CHCH_2$, $(CH_3)_3CCH_2CH_2$, $(CH_3)_2CHCH_2CH_2$, $CH_3CH_2CH(CH_3)\ CH_2$, $(CH_3CH_2)_2CHCH_2$, *c*-$C_5H_9CH_2$, *c*-C_6H_{11}.

A compound constituting a particularly advantageous embodiment of the invention is N-(3,3-diméthylbutyl)-L-aspartyl-L-phenylalanine methyl ester with the formula:

[see original for formula]

or N-(2-ethylbutyl)-L-aspartyl-L-phenylalanine methyl ester with the formula:

[see original for formula]

When Y is CH_3 and Z is CONHR", the compounds of the invention are alitame derivatives or alitame analogs and constitute another particularly advantageous embodiment of the invention. They then have the following general formula:

[see original for formula]

where R and R" meet the aforesaid definitions.

A compound constituting a particularly advantageous embodiment of the invention is N-(3,3-dimethylbutyl)-L-aspartyl-N-(dicyclopropylcarbinyl)-D-alaninamide with the formula:

[see original for formula]

or N-(3, 3-dimethylbutyl)-L-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide with the formula:

[see original for formula]

Thus, one of the characteristics of the invention is to substitute the 4-cyanophenyl, 2-cyanopyrid-5-yl, or 2-cyanopyrimidin-5-yl groups, as defined for R' in document EP-0 338 946, with groups that have no structural similarity and that have actually resulted in novel sweetening agents with a sweet dipeptide-derivative or dipeptide-analog chemical structure. In fact, when the new R' group is $CH(COOCH_3)CH_2C_6H_5$, the compounds of the invention are N-hydrocarbon aspartame derivatives, and when, for example, the new R' group is $CH(CH_3)CONHCH(c\text{-}C_3H_5)_2$, the compounds of the invention are N-hydrocarbon alitame analogs.

Thus, in the context of this invention, it was unexpectedly found that the sweetening power of aspartame was very greatly increased – up to several dozen times, depending on the nature of the R radical – by introducing a simple N-hydrocarbon group. For example, the compound of formula (IV) has a sweetening power approximately 10,000 times that of sucrose and approximately 80 times that of aspartame.

N-substituted aspartame derivatives have already been described (see, for example, J.M. Janusz, op cit). However, the sole known N-alkyl derivative, i.e., N,N-dimethyl-L-aspartyl-L-phenylalanine methyl ester, with the following formula:

[see original for formula]

has been described as having a bitter taste (R.H. Mazur *et al.*, J. Amer. Chem. Soc., 1969, 91, 2684-2691). This explains the negative attitude that has heretofore constituted an obstacle to searching for sweet N-hydrocarbon dipeptide derivatives, which were expected to be bitter.

It has further been demonstrated that the compounds characteristic of the invention is clearly more stable than aspartame under common conditions of use for food preparations. This advantage is all the more important, since one of the limits of the use of aspartame in some food preparations is its very poor stability in nearly neutral media, i.e., at a pH of approximately 7, a common pH of products such as dairy products, pastries, and other preparations that must be cooked at high temperatures.

We have also demonstrated that the compounds of the invention have improved stability in acid media, at a pH of approximately 3 – the pH of carbonated beverages – which is one of the major applications for sweeteners.

Thus, in an accelerated aging study by prolonged heating of a pH 3 aqueous solution at 70°C, it was shown that one of the compounds characteristic of the invention, compound (IV), has a half-life of approximately 55 hours. As a comparison, the half-life of aspartame under the same conditions is only approximately 24 hours, i.e., the compound according to the invention is 2.3 times more stable.

An identical accelerated aging test at pH 7 showed that the compound (IV) has a half-life of approximately 6 hours, while the half-life of aspartame under the same conditions is only 10 minutes, i.e., the product according to the invention is 36 times more stable. Comparable results were obtained with the other compounds characteristic of the invention.

Due to their sweetening intensity, another advantage of the compounds of the invention, compared to aspartame, is that when used in food products, they allow a very small quantity of active agent to be used. Consequently, the sometimes controversial presence in food products of certain components of aspartame, i.e., L-phenylalanine and methanol, can be greatly reduced. For example, in one liter of carbonated beverage, it will be possible to replace 550 mg of aspartame with approximately 7 mg of the compound (IV) of the invention, and, from a molecular perspective, to reduce the quantities of L-phenylalanine and methanol likely to be consumed by a factor of 100 (one hundred), while maintaining identical organoleptic qualities.

Likewise, it has been observed that an N-substitution in the alpha-amino group of alitame-type dipeptide analogs with N-hydrocarbon groups also results in compounds that have a more intense sweetening power. For example, the compound (VII), an N-substituted derivative of an alitame analog, has 2,500 times more sweetening power than sucrose, i.e., two times higher than the sweetening power of that same analog (EP-034 876).

The sweetening agents of this invention may be added to any edible product where a sweet taste is desirable, on condition they be added in proportions sufficient to achieve the desired level of sweetness. The optimal concentration for use of the sweetening agent will depend on diverse factors such as, for example, the sweetening power of the sweetening agent, the conditions of storage and use of the products, the specific components of the products, and the desired level of sweetness. Any qualified person may easily determine the optimal proportion of sweetening agent that should be used to obtain an edible product by performing routine sensory analyses. Depending on the sweetening power of the compound, the sweetening agents of this invention are generally added to the edible products in proportions from 0.5 mg to 20 mg of sweetening agent per kilogram or liter of edible product. Concentrated products will obviously contain larger quantities of sweetening agent and will then be diluted according to the final instructions for use.

The sweetening agents of this invention may be added in their pure form to the products to be sweetened, but, due to their intense sweetening power, they are generally mixed with an appropriate carrier or bulking agent.

Advantageously, the appropriate carriers or bulking agents are selected from the group comprising polydextrose, starch, maltodextrin, cellulose, methylcellulose, carboxymethylcellulose, and other cellulose derivatives, sodium alginate, pectins, gums, lactose, maltose, glucose, leucine, glycerol, mannitol, sorbitol, sodium bicarbonate, phosphoric, citric, tartaric, fumaric, benzoic, sorbic, and propionic acids, and their sodium, potassium, and calcium salts, and their equivalents.

In an edible product, the sweetening agents according to the invention may be used alone, as the sole sweetening agent, or in combination with other sweetening agents, such as sucrose, corn syrup, fructose, sweet dipeptide derivatives or analogs (aspartame, alitame), neohesperidin, dihydrochalcone, hydrogenated isomaltose, stevioside, L sugars, glycyrrhizin, xylitol, sorbitol, mannitol, acesulfame-K, saccharine and its sodium, potassium, ammonium, and calcium salts, cyclamic acid and its sodium salts, potassium, and calcium salts, sucralose, monellin, thaumatin, and their equivalents.

The compounds of this invention may be formulated by various methods already described in the literature. One of the preferred methods consists of condensing the dipeptide or dipeptide analog with the formula:

[see original for formula]
where n, Y, and Z are as defined above, with a hydrocarbon aldehyde having 4 to 13 atoms of carbon, and reducing the resulting imine *in situ*, with sodium cyanoborohydride using the reductive N-monoalkylation technique described by Ohfune *et al.* (Chem. Letters, 1984, 441-444). The reaction is carried out at ambient temperature in methanol.

The formulation of the dipeptide or dipeptide analog with the aforesaid formula uses the basic principles of peptide synthesis, i.e., protection and release of the amino and carboxyl groups of the precursor amino acids, as well as peptide activation and binding methods. These techniques are described in detail in many publications, including M. Bodanszky and A. Bodanszky, The Practice of Peptide Synthesis, Springer-Verlag, New York, 1984, 284 pp. If the dipeptide precursor is aspartame, this compound is of commercial origin.

The sweetening agents of the invention may also be salified with physiologically acceptable inorganic or organic acids or bases, which increase their solubility. Advantageously, these compounds are salified in the form of sodium, potassium, ammonium, calcium, or magnesium hydrochloride or salts.

In their acid or salified form, the compounds of the invention are purified using standard techniques such as recrystallization or chromatography. Their structure and purity are verified using standard techniques (thin layer chromatography, high performance liquid chromatography, infrared spectrometry, nuclear magnetic resonance, basic analysis).

The sweetening power of the compounds described in the examples was evaluated by a group of eight experienced individuals. The compounds, in an aqueous solution at variable concentrations, were compared to 2%, 5%, and 10% sucrose control solutions in taste tests. The sweetening power of the compound, tested in comparison to sucrose, reflects the weight ratio between the compound and sucrose at equal sweetening intensity, i.e., when the sweet flavors of the test compound solution and the sucrose control solution were considered by a majority of the individuals to have the same sweetening intensity.

The stability of the compounds of the invention and aspartame was measured by assaying (by high performance liquid chromatography, HPLC) the quantity of product remaining after accelerated aging in an acid medium (pH 3 phosphate buffer) or in a neutral medium (pH 7 phosphate buffer) at a temperature of 70°C. The stability of the test compound was evaluated by its half-life (50% degradation time).

The manner in which the invention may be prepared and the resultant advantages will be better understood with reference to the following sample embodiments.

EXAMPLES

Synthesis of N-(3,3-dimethylbutyl)-L-aspartyl-L-phenylalanine methyl ester, with the formula:

[see original for formula]

To prepare this compound, 4 g (39.8 mmol) of 3,3dimethylbutyraldehyde of commercial origin are added to a mixture in 50 cc of methanol, 10.6 g (36.2 mmol) of aspartame, and 1.6 g (25.3 mmol) of sodium cyanoborohydride. The solution is stirred for 24 hours at ambient temperature and then concentrated in a vacuum until dry. The residue is diluted in an aqueous solution of 1 N hydrochloric acid until the pH is approximately neutral. The precipitate is separated by filtration. The pellet is then vacuum dried and recrystallized twice in acetonitrile. This yields 9 g (62% yield) of N-(3,3dimethylbutyl)-L-aspartyl-L-phenylalanine methyl ester.

This compound has approximately 10,000 times the sweetening power of sucrose by weight, compared to a 2%, 5%, and 10% sucrose solution.

Compared to aspartame, an aqueous solution of 7 mg/L of the compound (IV) is equivalent in sweetening intensity to a solution of 550 mg/L of aspartame, i.e., approximately 80 times the sweetening power of aspartame.

By way of example, the sweetening power of several compounds according to the invention with the formula (III), obtained according to an experimental procedure similar to the one described above, which is easily available to a person skilled in the art, is, by comparison with a 2% sucrose solution, 500 times more intense than sucrose when R is a $(CH_3)_2CHCH_2$ group (IX), 2,000 times more intense than sucrose when R is the $(CH_3CH_2)_2CHCH_2$ group (X), 1,300 times more intense than sucrose when R is the $(CH_3)_2CHCH_2CH_2$ group (XI), 900 times more intense than sucrose when R is a $CH_3CH_2CH(CH_3)CH_2$ group (XII), 1,500 times more intense than sucrose when R is a c-$C_5H_9CH_2$ group (XIII), and 700 times more intense than sucrose when R is a *c*-C_6H_{11} group (XIV).

Likewise, the compound (VII) with the formula (VI), where R is $(CH_3)_3CCH_2CH_2$ and R" is $CH(c\text{-}C_3H_5)_2$, has 2,500 times more sweetening power than sucrose.

The attached Figure 1 shows a diagram comparing the stability curves of aspartame (Curve 1) and several compounds characteristic of the invention with the formula (III), such as, for example, the compound (IV) (Curve 2), the compound (IX) (Curve 3), or the compound (X) (Curve 4), obtained by accelerated aging by heating their solutions to 70°C in a pH 3 acid medium. Under these conditions, the half-life of aspartame is 24 hours, while the half-lifes of the compounds of the invention are 55 hours for the compound (IV), 35 hours for the compound (IX), and 96 hours for the compound (X), i.e., 1.5 to 4 times more stable.

The attached Figure 2 shows a diagram comparing the stability curves of aspartame (Curve 1), and the compounds (IV), (IX), and (X) (Curves 2, 3, and 4) of the invention, obtained by accelerated aging by heating their solutions to 70°C in a pH 7 neutral medium. Under these conditions, aspartame has poor stability (half-life of 10 minutes), while the half-lifes of the compounds of the invention are 6 hours for the compound (IV), 4 hours and 15 minutes for the

compound (IX), and 10 hours for the compound (X), i.e., 35 to 38 times more stable than aspartame.

CLAIMS

1. Compounds with the general formula:

[see original for formula]

where:
R is a hydrocarbon group with four to thirteen saturated or unsaturated carbon atoms, which may be cyclic, acyclic, or a combination;
n is equal to 1 or 2;
and R' is represented by the following formula:

[see original for formula]

where Y is selected from the group comprising $COOCH_3$, $COOC_2H_5$, CH_3, CH_2OH, $CON(CH_3)_2$, C_6H_5, 2-furyl, and H, and where Z is selected from the group comprising $CH_2C_6H_5$, C_6H_5, n-C_4H_9, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, COOfenchyl, and CONHR", where R" is selected from the group comprising CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH(CH_3)COOCH_3$, $CH(c\text{-}C_3H_5)_2$, $CH(c\text{-}C_3H_5)C(CH_3)_3$, fenchyl, 2,6-dimethylcyclohexyl, 2,2,5,5-tetramethylcyclopentyl, and 2,2,4,4-tetramethyl-3-thietanyl; and their physiologically acceptable salts.

2. Compounds according to Claim 1, wherein n is equal to 1.

3. Compounds according to Claim 1 or 2 with the following formula:

[see original for formula]

where R is preferably selected from the group comprising $CH_3CH_2CH_2CH_2$, $(CH_3)_2CHCH_2$, $(CH_3)_3CCH_2CH_2$, $(CH_3)_2CHCH_2CH_2$, $CH_3CH_2CH(CH_3)\ CH_2$, $(CH_3CH_2)_2CHCH_2$, c-$C_5H_9CH_2$, c-C_6H_{11}.

4. Compound according to Claim 3 consisting of N-(3,3-dimethylbutyl)-L-aspartyl-L-phenylalanine methyl ester with the formula:

[see original for formula]

5. Compound according to Claim 3 consisting of N-(2-ethylbutyl)-L-aspartyl-L-phenylalanine methyl ester with the formula:

[see original for formula]

6. Compounds according to Claim 1 or 2 with the formula:

[see original for formula]

where R is selected from the group comprising $CH_3CH_2CH_2CH_2$, $(CH_3)_2CHCH_2$, $(CH_3)_3CCH_2CH_2$, $(CH_3)_2CHCH_2CH_2$, $CH_3CH_2CH(CH_3)$ CH_2, $(CH_3CH_2)_2CHCH_2$, *c*-$C_5H_9CH_2$, *c*-C_6H_{11} and where R" is selected from the group comprising CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH(CH_3)COOCH_3$, $CH(c\text{-}C_3H_5)_2$, $CH(c\text{-}C_3H_5)C(CH_3)_3$, fenchyl, 2,6-dimethylcyclohexyl, 2,2,5,5-tetramethylcyclopentyl, and 2,2,4,4-tetramethyl-3-thietanyl.

7. Compound according to Claim 6 consisting of N- (3,3-dimethylbutyl)-L-aspartyl-N-(dicyclopropylcarbinyl)-D-alaninamide with the formula:

[see original for formula]

8. Compound according to Claim 6 consisting of N- (3,3-dimethylbutyl) -L-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide with the formula:

[see original for formula]

9. Application of the compounds according to any of Claims 1 to 8 as sweetening agents.

10. Process for formulation of a compound according to any of Claims 1 to 8, consisting of condensing a compound with the general formula:

[see original for formula]

where n, Y, and Z are as defined in Claim 1, with a hydrocarbon aldehyde having 4 to 13 atoms of carbon, and reducing the resulting imine *in situ*, with sodium cyanoborohydride.

FIG. 1

[see original for graph]

REMAINING PERCENTAGE

HOURS

COMPARATIVE STABILITY (pH 3, 70°C)

FIG. 2

[see original for graph]

REMAINING PERCENTAGE

HOURS

COMPARATIVE STABILITY (pH 7, 70°C)

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SEARCH REPORT
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FR 9213615
FA 480515

DOCUMENTS CONSIDERED PERTINENT		Claims concerned in the examined application	
Category	Description of the document with indication of the pertinent portions, if applicable		
X	JOURNAL OF ENZYME INHIBITION Vol. 5, No. 2, 1991, pages 133-149 A. Patel et al., 'Novel Inhibitors of Enkephalin-Degrading Enzymes III: 4-Carboxymethylamino-4-Oxo-3 (Phenylamino) Butanoic Acids as Enkephalinase Inhibitors' * table II, compounds 16 and 17 * * page 139, last paragraph - page 140, paragraph 1 * * page 141, paragraph 7 – page 142, paragraph 1 * ---	1-3	
A	EP-A-0 334 236 (MITSUI TOATSU CHEMICALS, INC.) * page 4, line 16 – line 17; claims * ---	1-3	
D,A	EP-A-0 338 946 (CLAUDE BERNARD UNIVERSITY) * claims; examples * ---	1-10	**TECHNICAL FIELDS SEARCHED (Int. Cl. 5)**
D,A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY Vol. 91, No. 10, May 7, 1969, Washington, DC, US pages 2684-2691 R.H. Mazur "Structure-Taste Relationships of Some Dipeptides' * page 2685, right column, paragraph 3; table VI * ---	1-10	C07K
A	EP-A-0 107 597 (CLAUDE BERNARD UNIVERSITY) * claims; examples * ---	1-10	

Search completion date	Examiner
AUGUST 24, 1993	Fuhr, C.K.B.

CATEGORY OF DOCUMENTS CITED

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